

PART ONE  
SYNTHESIS OF SOME 5-PHENYLQUINOLINES

PART TWO  
SYNTHESIS OF UNSYMMETRICAL DIARYL AMINES BY  
CONDENSATIONS OF AROMATIC NITROSO  
COMPOUNDS. 5-ANILINO-6-METHOXY-8-  
(3-DIETHYLAMINOPROPYLAMINO)  
QUINOLINE

PART THREE  
SYNTHESIS OF 2-(1-ETHYL-4-PIPERIDYLAMINO)-3-CYANO  
4-METHOXYMETHYL-5-AMINO-6-METHYLPYRIDINE

BY  
NELSON ROY EASTON  
A.B., Middlebury College, 1941

AN ABSTRACT OF A THESIS  
SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS  
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IN THE GRADUATE SCHOOL OF THE  
UNIVERSITY OF ILLINOIS, 1946

URBANA, ILLINOIS  
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## PART ONE

### SYNTHESIS OF SOME 5-PHENYLQUINOLINES

#### INTRODUCTION

Many substituted 8-aminoquinolines have shown high suppressive activity toward malarial parasites. Their activity was accompanied, however, by serious toxicity. It was believed that this toxicity might be due to an oxidative attack in position 5 of the quinoline nucleus, and it was considered possible that a phenyl group in that position would prevent oxidative attack at that point and hence reduce the toxicity of the drugs. A 5-phenyl-8-dialkylaminoalkylaminoquinoline was prepared to test this hypothesis.

#### DISCUSSION AND RESULTS

Chelintzev and Dubini (1) had shown that 8-hydroxyquinoline would react with Noval amine to form 8-(4-diethylamino-1-methylbutylamino)quinoline. It seemed that the hydroxyl group in 5-phenyl-8-hydroxyquinoline would undergo the same type of reaction, and since this compound had been previously prepared (2) it was the obvious starting material in the preparation of a 5-phenyl-8-dialkylaminoalkylaminoquinoline. The replacement of the hydroxy group of 5-phenyl-8-hydroxyquinoline with a dialkylaminoalkylamino group, however, was unsuccessful.

5-Phenyl-6-methoxy-8-(3-diethylaminopropylamino)quinoline was prepared in the following manner. *o*-Phenylphenol was condensed with benzenediazonium chloride (3) and the product was methylated, reduced to the amine, acetylated and nitrated. The *o*-nitro-acetylamino compound was submitted to the Skraup reaction and the product was hydrogenated and alkylated with 3-diethylaminopropyl chloride.

The intermediate nitration product was shown to have the nitro group in a position *ortho* to the acetylamino group

by hydrolysis to the free amine, reduction to the diamine and condensation with phenanthraquinone to form a phenazine derivative.

This material, 5-phenyl-6-methoxy-8-(3-diethylamino-propylamino)quinoline, was tested against avian malaria and found to be inactive. Thus it appears that the introduction of a phenyl group in the 5-position of an 8-aminoquinoline renders the molecule devoid of activity.

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## PART TWO

# SYNTHESIS OF UNSYMMETRICAL DIARYL AMINES BY CONDENSATIONS OF AROMATIC NITROSO COMPOUNDS. 5-ANILINO-6-METHOXY-8- (3-DIETHYLAMINOPROPYLAMINO)- QUINOLINE

## INTRODUCTION

Many intermediates in the syntheses of compounds useful as antimalarials or of materials suggested for testing as anti-malarials are unsymmetrical diaryl amines. These are usually prepared by the condensation of substituted amines with aromatic halides activated by *meta*-directing groups in the *ortho* or *para* positions.

Because of this general interest in unsymmetrical diaryl amines and the need for a synthesis of 5-anilino-6-methoxy-8-(3-diethylaminopropylamino)quinoline, a compound which was desired for testing as a possible antimalarial, a study has been made of the formation of anils by condensations of nitroso compounds. Such anils should be capable of reduction to secondary amines.

### DISCUSSION AND RESULTS

The condensation of *p*-mono- and di-alkylaminonitrosobenzenes with active methylene groups was first reported by Sachs (1, 2, 3). Euler (4), in an extension of this reaction, found that nitrosobenzene condensed with  $\alpha$ - and  $\beta$ -naphthol to form the phenylanil of the corresponding naphthoquinone. Kaufler and Suchanek (5) found that *p*-dimethylaminonitrosobenzene condensed with 9-anthrol in an analogous way and that 9-anthramine also could be made to react with *p*-dimethylaminonitrosobenzene in a similar manner.

In the synthesis of 5-anilino-6-methoxy-8-(3-diethylaminopropylamino)quinoline the condensation of nitrosobenzene with 6-methoxy-8-aminoquinoline and reduction of the product gave 5-anilino-6-methoxy-8-aminoquinoline (I). Alkylation of I with 3-diethylaminopropyl chloride gave 5-anilino-6-methoxy-8-(3-diethylaminopropylamino)quinoline. The structure of I was proved by degradation products and by an alternate synthesis from 5-chloro-6-methoxy-8-nitroquinoline and aniline.

It was found that 1-anilino-2-naphthylamine could be prepared by reduction of the product from the condensation of  $\beta$ -naphthylamine with nitrosobenzene. However, no products could be isolated when nitrosobenzene was condensed with  $\alpha$ -naphthylamine, *m*-anisidine, *m*-phenylenediamine or 6-aminoquinoline under the conditions used with 6-methoxy-8-aminoquinoline.

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## PART THREE

SYNTHESIS OF 2-(1-ETHYL-4-PIPERIDYLAMINO)-  
3-CYANO-4-METHOXYMETHYL-5-AMINO-  
6-METHYLPYRIDINE

## INTRODUCTION

The finding by Seeler (1) that pyridoxine in large doses inhibited the activity of quinine and atebine against *P. lophurae* in ducklings suggested a study of compounds with structures similar to pyridoxine. The present work was undertaken with the purpose of preparing 2-(1-ethyl-4-piperidylamino)-3-cyano-4-methoxymethyl-5-amino-6-methylpyridine and some of its derivatives.

## DISCUSSION AND RESULTS

2-(1-Ethyl-4-piperidylamino)-3-cyano-4-methoxymethyl-5-amino-6-methylpyridine was prepared by the condensation of 1-ethyl-4-aminopiperidine with 2-chloro-3-cyano-4-methoxymethyl-5-nitro-6-methylpyridine and hydrogenation of the product over platinum oxide catalyst. 2-Anilino-3-cyano-4-methoxymethyl-5-amino-6-methylpyridine and 2-(3-diethylaminopropylamino)-3-cyano-4-methoxymethyl-5-amino-6-methylpyridine were synthesized in a similar manner.

The reduction of 2-(1-ethyl-4-piperidylamino)-3-cyano-4-methoxymethyl-5-amino-6-methylpyridine to 2-(1-ethyl-4-piperidylamino)-3-aminomethyl-4-methoxymethyl - 5 - amino - 6 - methylpyridine was unsuccessful.

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## VITA

The author was born in Craftsbury Common, Vermont, on October 8, 1919. He attended the elementary school at Craftsbury Common and was graduated from Craftsbury Academy in 1937. In September of the same year, he entered Middlebury College and received from there the Bachelor of Arts degree in June, 1941. During the following two years, he was employed as a chemist in the research laboratory of Merck and Co., Inc., Rahway, New Jersey. In October, 1943, he entered the Graduate School of the University of Illinois as an assistant in chemistry, in which position he continued until June, 1944. From June, 1944, until March, 1946, he was employed as a special research assistant on the antimalarial program of the Committee on Medical Research of the Office of Scientific Research and Development. For the past semester he has served again as an assistant in chemistry.



